Remarks/Arguments:

This response accompanies a request for continued examination. Claims 1, 49, 66, 72, and 75 are amended herein, without the addition of new matter. Support for the amendments can be found throughout the specification, for example, page 13, lines 3-7, and page 15, lines 4-5. Claims 11 and 24 are canceled herein, without prejudice or disclaimer. The purpose of these amendments is to recite more specifically the concentration limitations of polyethylene glycol and poloxamer 188 which facilitate the lipid free, clear aqueous propofol solution which Applicants have invented.

Written Description

Claims 1, 11-12, 20, 23-37, 39-64, 66-68, and 71-78 stand rejected under 35 U.S.C. §112, first paragraph for alleged new matter with respect to the recitation of "less than 1% lipids." Applicants note that page 18, lines 15-31, of the specification describes preferred formulations of the invention as "substantially free of lipids," with "substantially free" defined further to include less than about 1%. Accordingly, the application describes the subject matter and Applicants respectfully urge that the rejection lacks proper foundation and should be withdrawn.

Obviousness

Claims 1, 11-12, 20, 23-37, 39-64, and 71-74 stand rejected as obvious over U.S. Pat. No. 4,452,817 (Glen) with WO 03/017977 (Meadows) in view of U.S. Pat. No. 6,140,374 (May) and U.S. Pat. No. 6,743,436 (Lee). Claims 75-78 are similarly rejected.

As an initial matter, Applicants note the Office Action indicates claims 75-78 stand rejected as obvious for the reasons applied to claims 49-64, 66-68, and 71-74. The Office Action does not, however, indicate that claims 66-68 are rejected. Clarification of the status of claims 66-68 is requested. For purposes of this response, Applicants treat claims 66-68 as if they had been rejected on grounds of obviousness for the reasons set forth in the Office Action, *i.e.*, Glen with Meadows in view of Lee and May.

The Office Action states that Glen teaches lipid-free propofol formulations lacking a surfactant (citing col. 2, lines 54-60 and example 10a), and propofol formulations with less than 15% excipients (citing Example 6a, col. 5, lines 26-30). Previous Office Actions are referred to for allegations that Meadows teaches using poloxamers in aqueous propofol compositions, that Lee teaches various concentrations of excipients, and that May teaches the use of antibacterial

agents. The Office Action suggests that the claimed invention is obvious as a simple combination and modification of existing prior art elements.

Applicant contends this rejection fails to establish *prima facie* obviousness. To establish *prima facie* obviousness, the office must determine the scope and content of the prior art, ascertain the difference between the prior art and the claims, and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Once the *Graham* factual inquiries are resolved, the office must determine whether the claimed invention would have been obvious to one of ordinary skill in the art guided by the principles described in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ (2007). MPEP 2142-2143. The office has not met this legal burden because the references on the whole, whether considered individually or in any combination, fail to teach or suggest all of the limitations of the claimed invention and because no reason has been established for one of skill in the art to combine and modify the teachings of the references to arrive at the claimed invention, much less to be able to predict the results of the combination.

(A) All of the limitations of the claimed invention are not taught or suggested by the references

The Office Action cites three formulations from Glen (theoretical formulation from col. 2, Example 6a, and Example 10a) as the basis for the rejection, suggesting that the secondary references provide claimed elements not found in Glen. Applicants disagree that all of the claimed elements are taught or suggested by this combination.

Beginning with Glen's theoretical formulation from column 2, it requires a minimum of 10% of a water-miscible solvent (excipient). Aside from the propofol and solvent, the remainder of the formulation is water. In contrast, the claimed invention calls for a minimum of about 2% of PEG and about 5% of poloxamer 188. Glen does not teach or suggest adding poloxamer 188 or PEG to the theoretical formulation. Moreover, adding these excipients to the theoretical composition cited by the Office Action would result in a composition with at least about 17% excipients, which exceeds the 15% recited by the claims. Accordingly, Glen does teach or suggest the claimed formulations.

None of the secondary references (Meadows, Lee, or May) supply the missing elements. The secondary references, taken together, do not teach or suggest aqueous propofol compositions having the claimed excipients at the claimed concentrations. Meadows does not teach or suggest to use PEG, nor to use poloxamer 188 without combination with other poloxamers. Lee does not teach or suggest to use poloxamer 188 in the absence of lipid, or

where the total excipient concentration is only up to 15%. May describes oil-based formulations, and does not teach or suggest aqueous propofol compositions with less than 1% lipid. Thus, the theoretical formulation from column 2 of Glen, alone or in combination with the teachings of Meadows, Lee, and May, does not teach or suggest all of the limitations of the claimed invention as a whole.

Moving next to the formulation described in Glen's Example 6a (column 5, lines 26-30), it contains 5% Myrj 52 as the only excipient, with propofol and water making up the rest of the formulation. Glen does not teach or suggest to add Poloxamer 188 or PEG to this formulation, and does not teach or suggest to add these excipients to compositions including Myrj 52 in general. Accordingly, the claimed formulations, which include PEG and poloxamer 188, are not taught or suggested by the primary reference.

The secondary references do not teach or suggest the missing elements. As set forth above, the secondary references do not teach or suggest aqueous propofol compositions having the claimed excipients at the claimed concentrations (at least about 2% PEG and at least about 5% poloxamer 188). Additionally, the secondary references do not teach or suggest propofol compositions including Myrj 52 in combination with poloxamer 188 and PEG, do not teach or suggest that these excipients should be included in formulations using Myrj 52, and do not teach the claimed concentrations of PEG and poloxamer 188. Thus, Example 6a of Glen, alone or in combination with the teachings of Meadows, Lee, and May, does not teach or suggest all of the limitations of the claimed invention.

Moving next to the formulation described in Example 10a of Glen, the formulation includes 10% propylene glycol, but does not include PEG. In addition, the formulation includes poloxamer 188 at a concentration of 10%, bringing the total excipient concentration to 20%, which far exceeds the 15% recited in the present claims. Accordingly, the claimed formulations are not taught or suggested by the primary reference.

None of the secondary references remedy the deficiencies of Glen. As shown above, the secondary references do not teach or suggest aqueous propofol compositions having the claimed excipients at the claimed concentrations (2-6% PEG and 5-9% poloxamer 188). The secondary references do not teach or suggest to substitute PEG for propylene glycol generally, and do not teach or suggest to use PEG in combination with poloxamer 188 within the claimed concentrations of these excipients and the total excipient concentration. Thus, Example 10a of Glen, alone or in combination with the teachings of Meadows, Lee, and May, does not teach or suggest all of the limitations of the claimed invention.

The foregoing discussion establishes that all of the limitations of the claimed invention are not taught or suggested by the art upon which the final rejection relies. The rejection is also in error because there would have been no reason for one of skill in the art to combine and modify any of the three cited formulations of Glen as needed to arrive at the claimed invention. Most importantly, the record is totally lacking with respect to any basis whatsoever that might have led one skilled in the art to have predicted the results of this combination, *i.e.*, a clear, aqueous propofol solution with less than 15 % excipients.

(B) No reason to combine and modify the cited references has been established

The theoretical formulation described in column 2 of Glen lacks PEG and poloxamer 188. To establish *prima facie* obviousness, the office must articulate a reason for one of skill in the art to add these excipients to the theoretical formulation as well as a reason to provide them at the claimed concentrations. No such reason is articulated in the pending rejection. Applicants submit further that the final rejection fails to suggest any basis for assuming, as the final rejection apparently does, that such reason would have been know to one skilled in the art. Nor does the reference provide a basis which would make applicants' invention, *i.e.*, a lipid-free, aqueous propofol solution with less than 15% excipients, predictable from the theoretical combination of references relied upon in the final rejection.

Glen does not teach or suggest adding PEG or poloxamer 188 to the theoretical formulation, presumably because solubility will be sufficiently effectuated by the appropriate concentration of the water-miscible-solvent taught by Glen, without the need to include PEG and poloxamer 188. Glen does not, however, identify any problems with the water-miscible solvent, and consequently, does not identify PEG or poloxamer 188 (or any other excipient) as potential solutions. Thus, the primary reference provides no reason to add PEG or poloxamer 188 to the theoretical formulation referenced in column 2.

The secondary references do not suggest that there is a problem with Glen's theoretical formulation, and thus do not give those of skill in the art reason to look for a solution in PEG and poloxamer 188 either. Meadows does not teach or suggest any problems with formulations such as Glen's theoretical formulation, or with water-miscible solvents generally. Thus, Meadows does not provide a reason to add elements of the cited art such as PEG and poloxamer 188 to the theoretical formulation. Meadows also does not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in the cited references to reach the claimed concentrations, even if these excipients are added to the theoretical formulation of

column 2. For example, Meadows teaches that only about 0.8% propofol can be solubilized in poloxamer 188 (see, Table 1a), and thus requires that poloxamer 188, if used, be combined with other poloxamers to dissolve propofol. Only poloxamer 188, however, is presently approved for use in humans and animals. Thus, there is no reason, based on the teachings of Meadows, to prepare aqueous propofol formulations using poloxamer 188 at concentrations of 5-9%. Meadows also fails to teach or suggest the use of PEG, alone or in combination with poloxamer 188, in propofol compositions.

Lee does not teach or suggest any problems with formulations such as Glen's theoretical formulation, or with water-miscible solvents generally. Thus, Lee does not provide a reason to add elements of the various cited references such as PEG and poloxamer 188 to the theoretical formulation. In addition, Lee does not provide any reason to modify the concentrations of PEG or poloxamer 188 described in the cited references to reach the claimed concentrations, even if these excipients are added to the theoretical formulation of column 2. Lee describes propofol compositions with poloxamer 188 within the presently claimed range, but only if lipids are used (Example 5, 2% glycerol), or if high levels of excipient are used (Example 7, 18% excipient). Lee provides no reason for one of skill in the art to reduce lipid concentration, and provides no reason to lower total excipient concentration, which is significant in light of the hydrophobic nature of propofol, and the difficulties demonstrated in the art in achieving an aqueous propofol composition with minimal excipients.

May does not teach or suggest any problems with formulations such as Glen's theoretical formulation, or with water-miscible solvents generally. Thus, May does not provide a reason to add elements of the various cited references such as PEG and poloxamer 188 to the theoretical formulation. May also does not provide any reason to modify the concentrations of PEG or poloxamer 188 even if these excipients are added to Glen's theoretical formulation of column 2. May does not teach or suggest aqueous propofol formulations, and does not teach or suggest to use poloxamer 188 and PEG in aqueous propofol formulations.

In addition, the Office Action does not provide any evidence to suggest that those of skill in the art would recognize a problem with the theoretical formulation that would give a reason to consider PEG and poloxamer 188 as a solution. Similarly, no evidence has been provided to show that those of skill in the art would recognize a problem with the concentrations of PEG and poloxamer 188 described in the cited art that would give rise to a reason to consider modifying their respective concentrations to arrive at the claimed concentrations. Accordingly, the knowledge in the art does not provide a reason to combine and modify the teachings of the cited art. And even if such problems were known, the art does not provide the artisan with a

solution, like applicants' unique combination, which could not have been predicted from that art.

Glen, Meadows, Lee, and May do not teach or suggest problems with propofol compositions formulated with water-miscible solvents, do not teach or suggest to add poloxamer 188 and PEG to a formulation prepared using a water-miscible solvent, do not teach or suggest to add these excipients at the claimed concentrations, and do not teach or suggest to maintain a total excipient concentration of less than 15%. Neither the cited references nor the knowledge available to those of skill in the art provide a reason to add PEG or poloxamer 188 to the theoretical formulation of column 2 of Glen, and more importantly, they do not provide a reason to modify the concentrations described in the cited art to provide them at the claimed concentrations.

The theoretical formulation described in Example 6a of Glen uses Myrj 52 as an excipient, and like the theoretical formulation of column 2 described above, lacks PEG and poloxamer 188. To establish *prima facie* obviousness, the statement of rejections must articulate a reason for one of skill in the art to add these excipients to the Example 6a formulation, as well as a reason to provide them at the claimed concentrations. Applicants submit that no such reason is even alleged, much less articulated.

Glen does not teach or suggest to add PEG or poloxamer 188 to the formulation of Example 6a, presumably because solubility will be sufficiently effectuated by Myrj 52, without the need to also include PEG and poloxamer 188. The reference is devoid of any indication of a problem associated with using Myrj 52 to prepare propofol formulations, and similarly devoid of any suggestion of a combination of PEG and poloxamer 188 (or other excipients) as a potential solution to such problems. Thus, the primary reference provides no reason to add PEG or poloxamer 188 to the formulation described in Example 6a.

Meadows does not teach or suggest any problems with aqueous propofol compositions formulated with Myrj 52 such as those taught in Example 6a, or with Myrj 52 generally. Thus, Meadows does not provide a reason to add elements of the cited art such as PEG and poloxamer 188 to the Example 6a formulation. For the reasons set forth above, Meadows also does not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in the cited references to reach the claimed concentrations, even if these excipients are added to a formulation such as that described in Example 6a.

Lee does not teach or suggest any problems with aqueous propofol compositions formulated with Myrj 52 such as those taught in Example 6a, or with Myrj 52 generally. Thus, Lee does not provide a reason to add elements of the cited art such as PEG and poloxamer 188

to Example 6a. For the reasons set forth above, Lee also does not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in its formulations or in formulations described by any of the cited references to reach the claimed concentrations, even if these excipients are added to a formulation such as that described in Example 6a of Glen.

May does not teach or suggest that there are any problems with aqueous propofol compositions formulated with Myrj 52 such as those taught in Example 6a, or with Myrj 52 generally. Thus, May does not provide a reason to add elements of the cited art such as PEG and poloxamer 188 to the Myrj containing formulations of Example 6a. For the reasons set forth above, May also does not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in the cited references to reach the claimed concentrations, even if these excipients are added to a formulation such as that described in Example 6a of Glen.

In addition, the Office Action does not provide any evidence to suggest that those of skill in the art would recognize a problem with the Myrj 52 formulation of Example 6a that would give rise to a reason to consider PEG and poloxamer as a solution to this problem. Similarly, no evidence has been provided to show that those of skill in the art would recognize a problem with the concentrations of PEG and poloxamer 188 described in the cited art that would give rise to a reason to consider modifying their respective concentrations to arrive at the claimed concentrations. Accordingly, the knowledge in the art does not provide a reason to combine and modify the teachings of the cited art.

Glen, Meadows, Lee, and May do not teach or suggest problems with propofol formulations prepared with Myrj 52, do not teach or suggest to add poloxamer 188 and PEG to Myrj 52-containing formulations, do not teach or suggest to add these excipients at the claimed concentrations, and do not teach or suggest to maintain a total excipient concentration of up to 15%. Thus, the cited references do not provide a reason to add PEG or poloxamer 188 to the formulation described in Example 6a of Glen, and more importantly, do not provide a reason to modify the concentrations described in the cited art to provide them at the claimed concentrations.

The formulation described in Example 10a of Glen does not use PEG, includes 10% propylene glycol, and uses a 20% total excipient concentration. To establish *prima facie* obviousness, the office must establish a reason for one of skill in the art to substitute PEG for propylene glycol, and a reason to lower the PEG and poloxamer 188 concentrations to arrive at the claimed concentrations. Applicants submit that neither reason has been established.

Glen does not teach or suggest to that PEG is an appropriate excipient to include in the formulation described in Example 10a, and does not teach or suggest to substitute PEG for

propylene glycol in this composition. This is significant because there are other formulations described by Glen in which it is indicated that propylene glycol or PEG could be used (see, *e.g.*, col. 3, lines 30-33). In addition, Glen does not teach or suggest lowering the excipient concentration below 20% in the presence of PEG or poloxamer 188, without including a significant concentration of lipids such as Cremophor. This underscores the difficulty in achieving a low-excipient, low-lipid, aqueous propofol formulation, and underscores that those of skill in the art at the time of the invention did not appreciate the synergistic effect of combining PEG and poloxamer 188 at the claimed concentrations to achieve the claimed compositions. Glen does not indicate that there is a problem with using 20% excipients, and does not indicate that there is a problem in using propylene glycol. Thus, the primary reference provides no reason to substitute PEG for propylene glycol, and provides no reason to lower the total excipient concentration of the formulation described in Example 10a.

The secondary references do not teach or suggest a problem with formulations that utilize propylene glycol or formulations that use 20% excipients, and thus do not give those of skill in the art reason to look for a solution in PEG and in lower excipient concentration. Meadows does not teach or suggest any problems with propofol compositions formulated with 10% propylene glycol and 20% total excipient concentration such as those taught in Example 10a of Glen. Thus, Meadows does not provide a reason to substitute elements of the cited art such as PEG for propylene glycol. For the reasons set forth above, Meadows also does not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in the cited references to reach the claimed concentrations, even if PEG is substituted for propylene glycol in a formulation such as that described in Example 10a.

Lee does not teach or suggest any problems with propofol compositions formulated with 10% propylene glycol and 20% total excipient concentration such as those taught in Example 10a. Thus, Lee does not provide a reason to substitute elements of the cited art such as PEG for propylene glycol. For the reasons set forth above, Lee also does not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in its disclosure or in the disclosure of any of the cited references to reach the claimed concentrations, even if a propylene glycol to PEG substitution is made in a formulation such as that described in Example 10a of Glen.

May does not teach or suggest that there are any problems with aqueous propofol compositions formulated with 10% propylene glycol and 20% total excipient concentration such as those taught in Example 10a. Thus, May does not provide a reason to substitute elements of the cited art such as PEG for propylene glycol. For the reasons set forth above, May also does

not provide any reason to modify the concentrations of PEG or poloxamer 188 as described in any of the cited references to reach the claimed concentrations, even if these excipients are added to a formulation such as that described in Example 10a of Glen.

The Office Action does not cite to any evidence to show that those of skill in the art would have recognized a problem with the formulation of Example 10a to which PEG and the claimed concentration of excipients would be a potential solution. Similarly, no evidence has been provided to show that those of skill in the art would recognize a problem with the concentrations of PEG and poloxamer 188 described in the cited art that would give rise to a reason to consider modifying their respective concentrations to arrive at the claimed concentrations. Accordingly, the knowledge in the art does not provide a reason to combine and modify the teachings of the cited art.

Finally, even if one skilled in the art were presented with some reason to try permutations and substitutions of selected parts of the cited art teachings relied upon in the final rejection, Applicants' final result of a clear, lipid free, aqueous propofol solution with less than 15% excipients, and the permutations and substitutions necessary to achieve that result were totally unpredictable. The references provide no basis for such predictability.

Accordingly, Applicants request reconsideration of applicants' claims, as amended. Upon such reconsideration, Applicants respectfully submit that all of these claims should be found allowable for all of the reasons indicated above and notification thereof is earnestly solicited. In order to advance prosecution of this application, the Examiner in charge of the application is requested to call one of the undersigned attorneys to discuss any further minor amendments deemed necessary to place this application in condition for allowance.

Respectfully submitted,

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